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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,643	10/20/2000	Pramod K. Srivastava	8449-073-999	8419

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/693,643	SRIVASTAVA, PRAMOD K.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,9,13,17,21,25-42,44,46 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,9,13,17,21,25-42,44,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The examiner of the application has changed. This case has now been transferred as of 7/17/2002. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.

2. The amendments filed 6/18/2002 are acknowledged and entered. Claims 1-3,5-8,10-12, 14-16,18-20,22-24,43,45, and 48-81 are canceled without prejudice. Claims 4,9,13,17,21,25-42,44, and 46-47 are pending and examined on the merits.

Information Disclosure Statement

3. The Information Disclosure Statement filed 7/1/02 (paper no. 7) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Election/Restrictions

4. Applicant's election with traverse of group IV in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the restriction requirement was improper. Upon further consideration, and in view of the persuasive arguments set forth by the applicant, claim 47 will be rejoined with group IV and will be examined on the merits.

Claim Rejections - 35 USC § 112

5. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 44, in the recitation of the term *"leukemias"*, it is unclear whether the claim limits the leukemias to the one listed in the claim or whether there are others not listed but also encompassed by the term. In addition, in

the recitation of the term *"heavy chain disease"*, it is unclear as to the metes and bounds of this term, because the specification does not provide an adequate description of the diseases which are encompassed by this term. Correction and/or clarification is required.

6. Claim 4,9,13,17,21,25-42, 44, and 46-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for eliciting an immune response treatment of cancer through the administration of heat shock proteins (hsp70, hsp90, gp96, and calreticulin only) in combination with a cancer cell antigenic component, does not reasonably provide enablement for treatment and prevention of cancer in humans through the co-administration of a vaccine and heat shock proteins (any). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Currently, as interpreted, a *"vaccine"* is an immunogen, wherein the composition comprises a component against which an immune response is desired (see page 13 lines 16-17) such as DNA or RNA vaccines.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond

that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claimed invention is drawn to a method of treating or preventing cancer in a patient by co-administering a vaccine composition comprising a component that displays the antigenicity of a cancer cell and a heat shock protein that is capable of inducing or increasing the immune response in a subject.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that heat shock proteins (HSP) are effective in treatment of cancer in mice through generation of immunogenic response to the hsp and its associated peptide complex (see for example Breloer *et al* J. Immunol 1999 Mar 15;162(6):3141-7). However, no where in the art does it show that HSPs are effective at treating or preventing disease in humans, especially cancer. Further, the combination of a vaccine (which is anything that can generates a desired immunogenic response) and a HSP has not been shown

in the art to be effective in the prevention of cancer. Furthermore, it has been shown that compounds or components that are used for the treatment of cancer are only effective for their therapeutic effect against cancer, and not as part of a prophylactic regimen. One such example found in the art, Evans *et al* (Q. J. Med 1999;92:299-307) teach that vaccines against cancer are not fully established, and it is stated that adjuvant therapy to prevent or delay disease still needs experimentation. Evans *et al* further state that such cancer vaccines are at best used as a therapeutic and not as a prophylactic and that *"the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction"* (see page 303 last paragraph).

The amount of direction or guidance present and the presence or absence of working examples: The specification describes the use of HSPs and their interaction with antigen presenting cells (APC) in the generation of a immunogeneic response and the role HSPs play as adjuvants to the generation of the immune response. However, the specification does not provide working examples that teach to one of skill in the art how to make and use HSP with vaccines to prevent the occurrence of cancer.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass *in vivo* administration of the claimed composition or vaccine to elicit either a therapeutic or prophylactic immune response and because the art teaches that the efficacy of cancer vaccines is highly unpredictable, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 4,9,13,27,30,33,42,44, and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Chen *et al* (Cancer Res. 2000 Feb 15;60(4):1035-1042). Claims 4,9,13,27,30,42,44,and 46 are drawn to a method of treating cancer comprising the administration to a subject a vaccine composition (as currently interpreted as being anything against which an immune response is desired, such as DNA vaccines) and a HSP or HSP-peptide, wherein the HSP is administered concurrently with the vaccine composition. Chen *et al* teach a DNA-based vaccine fused to a HSP effective in the reduction of tumor burden in mice (see page1039, figure 4A and B). Further, Chen *et al* disclose that the DNA-HSP vaccine induces and increase the immune response of the DNA based vaccine. Absent any evidence to the contrary, the HSP expressed by the cell disclosed by Chen *et al* can associate with a peptide, thereby forming an HSP-peptide complex. Further still, Chen *et al* suggest that the DNA-based HSP-fusion vaccine, although attempted to be directed to specific cells in an attempt to avoid MHC I pathways, cannot be directed solely to a single cellular location and the possibility that HSP-complexes presented via MHC I pathways cannot be ruled out (see page 1039 last paragraph).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 4,9,26-31,33, 42,44,and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al* (Cancer Res. 2000 Feb 15;60(4):1035-1042). Claims 4,9,26-31,42,44,and 46 are drawn to a method of treating cancer comprising the administration to a subject a vaccine composition and a HSP, wherein the HSP is administered before, concurrently, or after the vaccine composition. Chen *et al* teach a DNA-based vaccine fused to a HSP effective in the treatment of cervical cancer. Further, Chen *et al* disclose that the DNA-HSP vaccine induces and increase the immune response of the DNA based vaccine. However, Chen *et al* do not teach the administration of the HSP before or after the administration of the vaccine.

It would have *prima facie* obvious to one of ordinary skill at the time of the invention to attempt different administration methods or regimes, wherein one of skill would administer the HSP before or after the DNA vaccine. One of ordinary skill in the art would find it obvious because the administration of compounds can often precede or follow the administration of another compound, as part of a optimization method or protocol. One of ordinary skill in the art would have expected the same or similar amount of success because the administration of the HSP expressing DNA in Chen *et al* may or may not be translated before or after the translation of the E7 DNA.

11. Claims 4,9,13,17,21,25-42, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang *et al* (Int. J. Cancer 1999 Nov 12;83(4):532-40) in view of either Suzue *et al* (PNAS USA 1997 Nov; 94(24):13146-13151, IDS CL) or Chen *et al* (Cancer Res. 2000 Feb 15;60(4):1035-1042). Claims 4,9,13,17,21,25-42, and 46 are drawn to a method of treating cancer comprising the administration to a subject a vaccine that expresses a cancer associated immunogen (including but not limited to a live, attenuated vaccine, DNA or RNA vaccine, and an HSP composition, either alone or complexed with a peptide, wherein the vaccine is administered before, concurrently, or after the HSP composition. Yang *et al* teaches that both live and DNA vaccines that express or encode for tumor associated antigen (TAA) are effective in the immunotherapeutic treatment of cancer. Yang *et al* however, do not teach that this treatment should be combined with that of HSP either alone or complexed to a peptide. However, Chen *et al* teach a DNA vaccine fused to a HSP for adminstration as a cancer vaccine as described above. Suzue *et al* teach the use of HSPs (HSP70 in particular) complexed to peptides and their involvement in immunotherapeutic cancer treatment.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined a cancer antigen with a heat shock protein because Yang *et al* teach tumor associated antigens as cancer vaccines an Chen *et al* teach that HSP(s) enhance the potency of vaccines. Furthermore, because Yang *et al* teach that vaccines that express or encode TAA are effective in immunotherapeutic treatment and Chen *et al* teach that HSP(s) are effective in eliciting a potent immune response, the products were used individually in the prior art as

effective treatments of cancer and that separately they were effective. It would have been obvious to combine the two products of the prior art to practice the instant invention because the art teaches that individually they were effective on their own. One of ordinary skill in the art would have expected a reasonable amount of success in combining to two treatment methods because they were known to have an effect and that they were effective in eliciting an immune response for the treatment of cancer.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
August 8, 2002

Brenda Brumback
BRENDA BRUMBACK
Primary PATENT EXAMINER